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Hepatic Dysfunction in Two Sibs With Alström Syndrome: Case Report and Review of the Literature

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Alström syndrome is an autosomal recessive disorder (MIM No. *203800) characterized by retinal degeneration, obesity, deafness, noninsulin-dependent diabetes mellitus, and nephropathy. We report two sibs with Alström syndrome and hepatic dysfunction. The first sib developed elevations in liver enzymes at 29 years of age. Liver biopsy showed fatty liver, lymphocytic infiltration, and piecemeal necrosis. The second sib had had elevated γ-glutamyltransferase levels since she was 10 years old. She developed ascites, esophageal varices, and splenomegaly in her twenties. Cirrhosis was confirmed by autopsy; the patient was 26 years of age at death. Three Alström syndrome patients with hepatic dysfunction have been documented previously. No specific cause was identified for liver disease in any of the patients, including ours. Hepatic dysfunction appears to be a manifestation of Alström syndrome. Am. J. Med. Genet. 69:13–16, 1997.

KEY WORDS: Alström syndrome; liver cirrhosis; hepatitis; retinal degeneration; obesity; deafness; diabetes mellitus; nephropathy; variant

INTRODUCTION

In 1959, Alström described a condition characterized by retinal degeneration, obesity, deafness, noninsulin-dependent diabetes mellitus, and nephropathy. From the pedigree data of reported patients, autosomal recessive inheritance is indisputable [Goldstein and Fialkow, 1973]. Connolly et al. [1991] reported a patient with Alström syndrome who had hepatic dysfunction. We found two Alström syndrome patients with cirrhosis discussed in the Japanese literature [Ikeda et al., 1974; Horiuchi et al., 1976]. Investigations had failed to elucidate a viral, autoimmune, or metabolic pathogenesis in these patients. We report here on two sibs with Alström syndrome; the sister developed liver cirrhosis and the brother had nonspecific hepatitis associated with fatty liver.

CLINICAL REPORT

Patient 1

K.Y. was the product of a normal pregnancy and delivery. There was no parental consanguinity and no family history of diabetes mellitus or liver disease, except for his younger sister (patient 2). During his infancy, the patient was noticed to have poor visual acuity and obesity. At age 10, he developed polyuria, polydipsia, and glucosuria. When the patient was first seen by us, his height was 142.2 cm (50th centile) and his weight was 56 kg (over 97th centile). Acanthosis nigricans was noticed in the axillae and the antecubital area. There was no polydactyly. Pubic hair was present, and penis was at Tanner stage II. Testes were 1 ml bilaterally. Urine glucose was 3+ and ketone 1+. An oral glucose tolerance test showed overt diabetes mellitus with exaggerated insulin secretion. A fundoscopic examination demonstrated retinal degeneration. An audiogram showed sensorineural hearing loss. IQ was 77, and karyotype 46,XY. Testis biopsy showed no spermatogenesis. Plasma testosterone level was 15 ng/dl, which increased to 144 ng/dl after human chorionic gonadotropin (HCG) administration. Responses of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to LH-releasing hormone (LHRH) administration were normal. Triidothyronine, thyroxine, thyroid-stimulating hormone (TSH), urine 17-ketosteroids (17-KS), 17-hydroxycorticosteroids (17-OHCS) were normal. The patient was diagnosed as having Alström syndrome on the basis of retinal degeneration, diabetes mellitus, obesity, sensory hearing loss, and hypogonadism. He was managed by diet and an oral hypoglycemic agent. A renal biopsy performed when the patient was 15 years of age because of elevated plasma creatinine levels (1.5 mg/dl) showed interstitial fibrosis, glomerular hyalinosis, and tubular atrophy.

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Urine osmolality after desmopressin administration was 834 mOsm/kg. When he was 29 years old, the patient's liver enzyme levels were noticed to be high: aspartate aminotransferase 56 IU/liter, alanine aminotransferase 110 IU/liter, and γ-glutamyltransferase 174 IU/liter. He was admitted for liver biopsy. On admission, weight was 57.4 kg (40th centile) and height 155 cm (<3rd centile). Laboratory data included total protein 8.3 g/dl, total bilirubin 1.3 mg/dl, lactate dehydrogenase 140 IU/liter, alkaline phosphatase 334 IU/liter, cholinesterase 505 IU/liter, ammonia 27 mmol/liter, urea nitrogen 27.9 mg/dl, creatinine 1.5 mg/dl, uric acid 7.3 mg/dl, glucose 215 mg/dl, total cholesterol 173 mg/dl, and triglyceride 175 mg/dl. Prothrombin time and partial thromboplastin time were normal. Hepatitis B surface antigen and antibody, antihepatitis C antibody, and antihepatitis A antibody were negative. Ceruloplasmin was 27 mg/dl, copper 86 mg/dl, and α_1-antitrypsin 215 mg/dl. Antinuclear antibody titer was less than 1:40, plasma lactic acid 5.0 mg/dl, and pyruvic acid 0.89 mg/dl. Abdominal ultrasonography demonstrated fatty liver. Liver biopsy showed fatty vacuoles and intranuclear vacuolation in some hepatocytes, the findings being compatible with fatty liver (Fig. 1a). In addition, inflammatory infiltrates in the parenchyma and the portal area and perivenular fibrosis and mild piecemeal necrosis were observed (Fig. 1a).

Patient 2

This girl was the sister of patient 1. Poor visual acuity and obesity were noted from infancy. Her psychomotor development was normal. At age 9 years, she was seen for polyuria and polydipsia. Her height was 133.7 cm (75th centile) and weight 38.8 kg (over 97th centile).

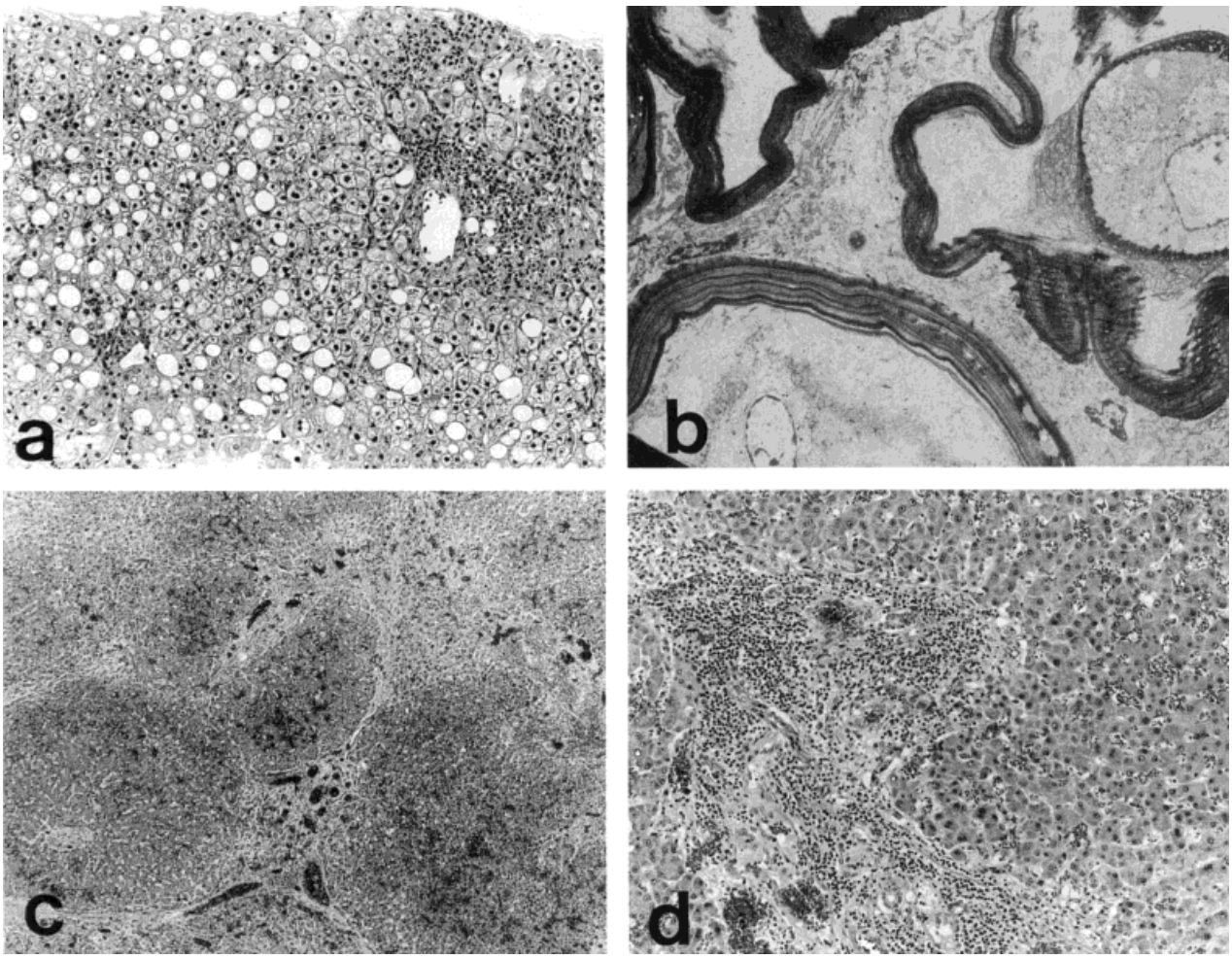

Fig. 1. Biopsy and autopsy findings in patients 1 and 2. **a:** Liver biopsy of patient 1 showing hepatocytes with fatty vacuoles and inflammatory infiltrates, perivenular fibrosis, and eroded limiting plate. ×120. **b:** Electron microgram of kidney autopsy specimen of patient 2 showing an abnormally thickened and layered basement membrane. ×2,000. **c:** Liver autopsy of patient 2 showing nodules of varying size and fibrous septa. ×30. **d:** Liver autopsy of patient 2 showing piecemeal necrosis, fibrosis, marked lymphocytic infiltration, and regenerative nodule of hepatocytes ×90.

Physical findings were unremarkable, except for acanthosis nigricans of the axillae. She had no polydactyly or other malformations. Urinalysis showed 3+ glucose. An oral glucose tolerance test showed hyperglycemia and hyperinsulinemia. A fundoscopic examination documented retinal degeneration. An audiogram showed sensorineural hearing loss. IQ was 90. Responses to LHRH loading test were within normal limits. Triidothyronine, thyroxine, TSH, urine 17-KS, and 17-OHCS levels were normal. She was started on diet therapy, and urine glucose became undetectable. At that time, a Fishberg test showed urine specific gravity of 1.021. She was discharged home with the diagnosis of Alström syndrome on the basis of retinal degeneration, diabetes mellitus, obesity, and sensory hearing loss. She had menarche at age 10 years, and her cycles had been regular since then. Therapy with an oral hypoglycemic agent was started at age 13 years, and insulin therapy at age 17 years. At age 23 years, she was admitted because of abdominal distension and nausea. Ascites was noted on abdominal ultrasonography. Her symptoms subsided with rest and diuretic therapy. At age 24 years, she was admitted because of hematemesis and received a blood transfusion. At age 25 years, continuous ambulatory peritoneal dialysis was initiated because of renal failure. At age 26 years, she had tarry stool and hematemesis and was admitted. There was no jaundice or anemia. Her abdomen was soft but distended with dialysis fluid. The liver and spleen were not palpable. There was tenderness in the epigastric area. Laboratory data included white blood cells 9,500/μl, hemoglobin 14.5 g/dl, hematocrit 44.2%, platelets 82,000/μl, total protein 6.1 g/dl (albumin 50.8%, α_1-globulin 3.6%, α_2-globulin 8.6%, β-globulin 7.4%, and γ-globulin 29.6%), total bilirubin 1.0 mg/dl, lactate dehydrogenase 172 IU/liter, aspartate aminotransferase 35 IU/liter, alanine aminotransferase 12 IU/liter, alkaline phosphatase 520 IU/liter, γ-glutamyltransferase 224 IU/liter, cholinesterase 1,101 IU/liter, urea nitrogen 37.4 mg/dl, creatinine 8.3 mg/dl, uric acid 5.2 mg/dl, glucose 130 mg/dl, total cholesterol 133 mg/dl, triglyceride 109 mg/dl, and C-reactive protein 1.21 mg/dl. Prothrombin time and partial thromboplastin time were normal. Hepatitis B surface antigen and antibody, hepatitis B core antibody, and antihepatitis C antibody were negative. Antinuclear antibody titer was less than 1:40. Abdominal ultrasonography showed splenomegaly, and an endoscopic examination disclosed esophageal varices. Review of the previous records revealed that her γ-glutamyltransferase level had been increasing since she was 10 years old. She was started on cimetidine therapy. Epigastralgia and hematemesis subsided, but tarry stool persisted. During admission, she developed pneumonia and died of respiratory failure. Autopsy findings included liver cirrhosis, splenomegaly, esophageal varices, bronchopneumonia, atherosclerotic changes in the aorta and coronary and peripheral arteries, and a sclerosed kidney. Light and electron microscopic findings for the kidney and skin were compatible with Alström syndrome; basement membranes were thickened, layered, wrinkled, and widened (Fig. 1b). In the liver, diffuse nodules 3–9 mm in diameter were present macroscopically. Under the light microscope, fibrosis was marked, delimiting the boundary of regenerative nodules (Fig. 1c). The lobules were markedly remodeled. At the higher magnification, changes similar to those caused by chronic active hepatitis were observed. Thus, the limiting plates of hepatic cells were destroyed. Dense fibrosis and marked lymphocytic infiltration were seen in the Glisson's sheath (Fig. 1d). Electron microscopic examination showed no specific changes in basement membrane or organelles.

DISCUSSION

Liver involvement in Alström syndrome was first described by Connolly et al. [1991]. Their 11-year-old patient developed hepatic dysfunction at age 8 years. No viral, autoimmune, or metabolic etiology was identified. Histopathological examinations disclosed changes similar to those seen in chronic nonspecific active hepatitis, i.e., lymphocytic portal inflammation and mild piecemeal necrosis of the periportal hepatocytes. The patient was treated with prednisone, followed by azathioprine. Serum aspartate aminotransferase and γ-glutamyltransferase levels were ameliorated, but a repeat biopsy demonstrated similar findings. In view of this, Connolly et al. [1991] postulated that nonspecific hepatitis may be another manifestation of Alström syndrome. In our patient 1, elevated liver enzyme levels were noted when he was in his late twenties. A histopathological examination of the liver showed fatty liver. In addition, lymphocytic infiltration and piecemeal necrosis were observed. In patient 2, liver cirrhosis was confirmed by autopsy. Her γ-glutamyltransferase level had been high since age 10 years, similar in age to Connolly's case. Her symptoms for cirrhosis, such as ascites, splenomegaly, and esophageal varices, became evident in her twenties. No known cause for cirrhosis was identified. Lymphocytic infiltrates and destruction of limiting plates were similar to those found in her sib and in Connolly's patient. The symptoms of diabetes, nephropathy, and deafness in patient 1 were milder than those in patient 2. Thus, fatty liver and nonspecific hepatitis in patient 1 may progress to cirrhosis.

Review of the Japanese literature revealed two patients with Alström syndrome who had liver cirrhosis. A patient reported by Ikeda et al. [1974] was a 27-year-old Japanese man with situs inversus. Liver biopsy showed biliary cirrhosis, the pathogenesis of which was unidentified. The other, a female patient, reported by Horiuchi et al. [1976], had hepatosplenomegaly, and was diagnosed with cirrhosis by liver biopsy at age 23 years. She died of hemorrhage from an esophageal varix at 25 years of age. No causes of cirrhosis were identified. Table I summarizes the findings in five Alström syndrome patients, including our cases, with hepatic dysfunction. All patients were relatively young when liver dysfunction was first detected. They all had retinal degeneration, nerve deafness, noninsulin-dependent diabetes, and obesity in childhood. Although necroinflammatory infiltrates or progression to cirrhosis is described in obesity-induced fatty liver, this is

TABLE I. Clinical Findings in Five Alström Syndrome Patients With Hepatic Dysfunction*

Clinical findings	Patient 1	Patient 2	Connolly et al. [1991]	Ikeda et al. [1974]	Horiuchi et al. [1976]
Age (years)	29	26	11	27	25
Sex	Male	Female	Female	Male	Female
Retinal degeneration	+	+	+	+	+
Obesity (degree)	+ (+17%)	+ → −	+ (+1–2 SD)	+ (+20%)	+ (+50%)
NIDDM	+	+	+	+	+
Nephropathy	+	+	−	−	−
Nerve deafness	+	+	+	+	+
Acanthosis nigricans	+	+	+	ND	ND
Hypogonadism	+	−	ND	+	−
Hypertriglyceridemia	−	−	+	−	+
Liver dysfunction	+	+	+	+	+
Diabetes insipidus	−	−	ND	ND	ND
Hyperuricemia	−	−	−	−	ND
Mental retardation	−	−	+ Mild	−	Borderline
Polydactyly	−	−	−	−	−
Affected sibship	+	+	−	−	−
Parental consanguinity	−	−	−	+	−
Others				Situs inversus	

*ND, not described.

usually limited to patients over 40 years of age, who are overweight by more than 120% and who have hypertriglyceridemia [Gholson and Bacon, 1992]. None of these five patients fits into this category. Fatty liver is also commonly associated with noninsulin-dependent diabetes. However, cirrhosis strictly attributable to diabetes has rarely been reported [Gholson and Bacon, 1992].

The possibility that hepatic dysfunction is an incidental complication in patients with Alström syndrome cannot be ruled out. However, the association of a rare syndrome with liver cirrhosis at a young age without known causes suggests that hepatic lesion is a systemic manifestation of Alström syndrome. Also, the occurrence of hepatic dysfunction in both of our sib cases may support our hypothesis. Nonspecific hepatitis seen in the two Alström syndrome patients may be an early expression that eventually progresses to cirrhosis. It remains to be seen whether the disorder in our patients belongs to a variant of Alström syndrome.

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